wherein X is R_1-$(R_2)_n$;

R_1 is C_1-C_{20} alkyl, C_4-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_2 is hydroxyl, thiol, keto, carboxyl, or amino;

either one of T_3 and T_5 is OH, a hydroxyl blocking group, phosphate or an activated phosphate group and the other of T_3 and T_5 is a nucleotide, or both T_3 and T_5 are nucleotides; and

n is an integer from 0 to about 6.--

REMARKS

By way of this amendment, claims 9 and 10 have been amended and new claims 26 and 27 added. Accordingly, claims 9, 10, and 15-27 are pending in this patent application.

Claims 9-10 and 15-25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an enabling disclosure. (Office Action at page 3). The Office Action asserts that Applicants have not enabled compounds wherein the 2'-O moiety comprises "exceptionally bulky groups," such as, for example, "carbocycles, heterocycles, and aryl groups." (Office Action at page 3). Applicants respectfully request reconsideration of this rejection, as there is no reason of record to believe that persons skilled in the art would not be able to make and use the claimed compounds.

The first paragraph of § 112 requires that the disclosure of a patent application be such that persons skilled in the art, having read the patent application, would be able to

practice the inventions described by the claims. That is, the disclosure should be one that enables persons skilled in the art to make and use the claimed inventions. There is no legal requirement that this be done in any particular manner; an enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology. *In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Moreover, a patent application must be deemed to be enabling unless there is reason to doubt the truth of statements contained in the patent application relating to making and using the invention. *Id.* Furthermore, any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). No such evidence or reasoning has been provided. If the assertion set forth in the Office Action is based on a reference or information known to the Examiner, Applicants respectfully request that the reference(s) be identified or a declaration pursuant to 37 C.F.R. § 1.107(b) be provided to support this position.

Significantly, the Office Action does not dispute that one skilled in the art would be able to make and use the claimed compounds. Rather, the Office Action asserts that one of ordinary skill in the art "would not accept that bulky 2'-O-substituents, particularly those close to the 2'-oxygen and

attached to each ribose moiety in a polynucleotide would yield a probe that could reasonably be expected to hybridize effectively." (Office Action at page 3). However, the possibility that certain of Applicants' claimed compounds (*i.e.*, those having the relatively large substituents identified in the Office Action) may exhibit less than optimal hybridization does not render Applicants' specification non-enabling. It is not the function of the claims to specifically exclude less than optimal compounds or, for that matter, even inoperative compounds. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 U.S.P.Q. 409 (Fed. Cir. 1984). Indeed, Applicants' claims do not require that **each** ribose moiety in the recited polynucleotides bear a 2'-substituent, much less one of the "bulky" substituents identified in the Office Action. There is no reason to believe that the presence of such substituents at selected positions will render the claimed compounds inoperative. Further, the Office Action incorrectly asserts that there is no teaching in the specification with regard to the length of a tether that will accommodate a polycyclic 2'-O structure. (Office Action at page 3). Page 3 of the specification, for example, clearly identifies compounds wherein "R_1 is C_3-C_{20} alkyl, C_4-C_{20} alkenyl, C_2 to C_{20} alkynyl." One skilled in the art would clearly be able to prepare compounds having 2'-O polycyclic structures having any of the recited tethers and evaluate them according to the procedures taught by Applicants (in, for example, Examples 49A, 49B, 50A,

and 50B) without undue experimentation. Thus, one skilled in the art would have no reason to doubt that the claimed compounds would function as taught by Applicants. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Claims 9-10 and 15-25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Buhr, *et al.*, U.S. Patent No. 5,466,786 (hereinafter referred to as the "Buhr patent") (Office Action at page 4), taken alone or as combined with Kikuchi, *et al.*, Chem. Abstract No. 110:24228w (hereinafter referred to as the "Kikuchi reference"). Applicants respectfully request reconsideration of this rejection, as the Buhr patent clearly fails to teach or suggest Applicants' claimed compounds.

The Office Action suggests that the subject matter of independent claims 9 and 10 would have been obvious to one of ordinary skill in the art because the Buhr patent provides a generic description of substituted 2'-O-alkyl-, 2'-O-alkenyl-, and 2'-O-alkynyl nucleosides wherein the substituents are hydroxy, amino, or thiol. (Office Action at page 4). Applicants have traversed this rejection by canceling such compounds from claims 9 and 10. Nevertheless, Applicants request reconsideration of the rejection in view of the presentation of the "canceled" compounds in claims 26 and 27, as the Buhr patent cannot be fairly said to place these compounds in the possession of the public, as required by § 103. *In re Payne*, 203 U.S.P.Q.

245, 255 (C.C.P.A. 1979) (references relied upon to support rejection under § 103 must place the claimed invention in the possession of the public).

Although the Buhr patent provides a generic discussion of 2'-O-substituted purines and pyrimidines, it is noteworthy that the patent fails to provide syntheses for any 2'-O-substituted compounds other than one specific type of 2'-O-substituted pyrimidine -- 2'-O-substituted cytidine. The Buhr patent provides no teaching of how to prepare other 2'-O-substituted nucleosides, much less a teaching of how to prepare the 2'-O-substituted purines (*i.e.*, 2'-O-substituted guanines and 2'-O-substituted 2-aminoadenines) to which the present claims are directed. (*See*, Example 3 of the Buhr patent). Accordingly, the Buhr patent does not place Applicants' claimed compounds in the possession of the public.

In fact, the prior art indicates that those skilled in the art would not consider the Buhr disclosure relating to pyrimidines enabling for Applicants' claimed purine compounds. For example, Sproat, *et al.*, (*Nuc. Acids Res.*, **1991**, *19*, 733) teaches that alkylation procedures which successfully alkylated pyrimidines could not be applied to purines. (*See*, page 733, first column). Those skilled in the art would have further reason to doubt that the alkylation procedures employed in the Buhr patent could be applied to Applicants' claimed compounds, as the reference which Buhr identifies as disclosing those

procedures (Inoue, *et al.*, *Nuc. Acids Res.*, 1987, *15*, 6131; hereinafter referred to as the "Inoue reference") teaches that the procedures are for the production of 2'-O-methyl derivatives of ribonucleosides other than guanosine. Indeed, the Inoue reference states that:

> 2'-O-Methyl derivatives of the common ribonucleosides ***except for guanosine*** were synthesized via the 2'-O-methylation of appropriately-protected nucleosides with CH_3I in the presence of Ag_2O.

(*See*, page 6131, introduction, emphasis added). One skilled in the art having examined the methodology of the Buhr patent, as well as the Inoue reference cited therein, would not readily believe that Applicants' 2'-O-substituted compounds could be prepared in the same manner as 2'-O-substituted cytidine compounds. In view of the difficulties inherent in preparing 2'-O-substituted purines (and the Buhr patent's failure to provide any synthetic methodology therefor), it cannot reasonably be said that the Buhr patent renders the claimed compounds obvious. Indeed, persons of ordinary skill the art skilled would find Applicants' invention surprising and non-obvious. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

The Kikuchi reference does not cure the deficiencies of the Buhr patent. The Kikuchi reference merely describes oligonucleotides which include 2-aminoadenosine. The Kikuchi

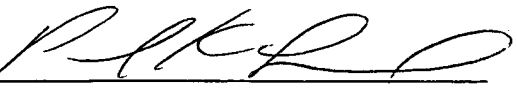
reference does not teach that sugar-substituted 2-aminoadenosine -- much less 2'-O-substituted 2-aminoadenosine -- can be prepared or used in the manner taught by Applicants. Accordingly, combination of the Buhr patent and Kikuchi reference would not have placed Applicants' claimed compounds in the possession of the public. In view of the deficiencies of these references, it cannot reasonably be said that combination of the Buhr patent and Kikuchi reference renders the claimed 2'-O-substituted 2-aminoadenosine compounds obvious. Accordingly, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 103.

Claims 9-10, and 15-25 stand provisionally rejected for alleged obviousness-type double patenting in view of claims 1-8, 62-63, and 69-72 of copending application Serial No. 08/373,298. Applicants request that resolution of this provisional rejection be deferred pending withdrawal of all other bases for rejection.

Applicants submit that the claims patentably define the invention over the applied art and are otherwise in condition for

ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,



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